Dendritic cell vaccination combined with CTLA4 blockade in patients with metastatic melanoma.

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Public Summary:
Dendritic cells (DC) are a type of immune cell that when exposed to a tumor antigen are thought to stimulate T cells and activate antitumor immunity. Cytotoxic T Lymphocyte-associated antigen 4 (CTLA4)-blocking antibodies act by releasing a key negative regulatory pathway on T cells, thereby activating the T cells. In this study, we tested the combination of tumor antigen exposed DC and CTLA4 antibodies in a phase I clinical trial in patients with advanced melanoma. DC from each patient were taken out of the patient, pulsed with the tumor antigen MART-1(26-35) peptide in the lab and infused back into the patient. At the same time, the patient was administered a dose escalation of the CTLA4-blocking antibody tremelimumab. Sixteen patients were accrued to five dose levels. Primary end points were safety and immune effects; clinical efficacy was a secondary end point. Dose-limiting toxicities of grade 3 diarrhea and grade 2 hypophysitis developed in two of three patients receiving tremelimumab at 10 mg/kg monthly. Four patients had an objective tumor response, two partial responses and two complete responses, all melanoma free between 2 and 4 years after study initiation. There was no difference in immune monitoring results between patients with an objective tumor response and those without a response. Exploratory gene expression analysis suggested that immune-related gene signatures, in particular for B-cell function, may be important in predicting response. In summary, the combination of MART-1 peptide-pulsed DC and tremelimumab results in objective and durable tumor responses at the higher range of the expected response rate with either agent alone.

Scientific Abstract:
PURPOSE: Tumor antigen-loaded dendritic cells (DC) are believed to activate antitumor immunity by stimulating T cells, and CTL-associated antigen 4 (CTLA4)-blocking antibodies should release a key negative regulatory pathway on T cells. The combination was tested in a phase I clinical trial in patients with advanced melanoma. EXPERIMENTAL DESIGN: Autologous DC were pulsed with MART-1(26-35) peptide and administered with a dose escalation of the CTLA4-blocking antibody tremelimumab. Sixteen patients were accrued to five dose levels. Primary end points were safety and immune effects; clinical efficacy was a secondary end point. RESULTS: Dose-limiting toxicities of grade 3 diarrhea and grade 2 hypophysitis developed in two of three patients receiving tremelimumab at 10 mg/kg monthly. Four patients had an objective tumor response, two partial responses and two complete responses, all melanoma free between 2 and 4 years after study initiation. There was no difference in immune monitoring results between patients with an objective tumor response and those without a response. Exploratory gene expression analysis suggested that immune-related gene signatures, in particular for B-cell function, may be important in predicting response. CONCLUSION: The combination of MART-1 peptide-pulsed DC and tremelimumab results in objective and durable tumor responses at the higher range of the expected response rate with either agent alone.